REMARKS

Reconsideration of this application is requested. Claims 35-43 will be active in the application subsequent to entry of this Amendment.

The specification has been amended to address the issues raised by the examiner on pages 2 and 3 of the Official Action and also to include a cross reference to an earlier PCT application of which this is a continuation.

The claims have been amended in order to more particularly point out and distinctly claim that which applicants regard as their invention, to define preferred aspects of the invention and to respond to the issues raised on pages 3-6 of the Official Action.

In the Official Action questions are raised concerning applicant's intent with regard to administration of the active ingredient according to the claimed method. The gist of the present invention resides in the administration of alkaline sphingomyelinase (ASmase herein) (description, page 1, first paragraph). This invention can be put into practice either by administering the ASmase per se, or by administering bacteria possessing ASmase (page 4, second paragraph). The bacteria can be administered either live (as they are or lyophilized) or dead (sonicated) or extracts thereof may be used, provided the extracts contain ASmase (page 4, second paragraph). In a preferred embodiment, the ASmase is administered by ingesting the bacteria and these bacteria can be live, sonicated or lyophilized (page 6, line 20).

Attention is invited to the statement in the description (page 4, line 8) *"It has now been found, surprisingly, that some bacteria possess high levels of alkaline sphingomyelinase, and that their ingestion can be beneficial for the host."*

From the description of the invention it is clear to the skilled reader that, in the case ASmase is administered by ingestion of bacteria, that certain bacteria containing ASmase will be administered. The strains cited in the application are those provided with this kind of enzyme, but any other bacteria found to be provided with the enzyme will fall

within the claims. In the example, it is shown how to determine the presence of ASmase activity in the bacteria, thus enabling the skilled person to easily verify if a certain strain will fall within the claims. It will be also appreciated that no acidic Smase and some activity of neutral SMase were detected.

It is not necessary to isolate alkaline ASmase from acidic Smase and neutral SMase, since they are naturally present in the body. What matters is to administer alkaline ASmase. Combinations of species are contemplated in the application, but they are not essential. Only one strain can be used.

The objection as to an uncertain unindentified component used in order to deactivate other forms of sphingomyelinase is readily case aside by the skilled reader by resorting to his own knowledge. Acidic sphingomyelinase is absent from bacteria used in the invention. Since intestinal pH is alkaline, neutral sphingomyelinase, if any, is inactive. In any case, the description provides sufficient teachings on page 11, lines 20-23, on how to neutralize neutral SMase.

Certain claim terminology is also questioned in the Official Action and applicants have taken the examiner's comments into account in preparing the new claims, to the extent relevant to the disclosed subject matter and current US PTO practice. The terms "prophylactically effective" or "therapeutically effective" have been used in accordance with past and current US PTO practice, since in 223 US patents have been granted with the term "prophylactically effective" (see US 6,555,141, for example). As for the term "therapeutically effective", there are more than 10,000 U.S. patents. The Examiner is invited to explain where there is the difference between the present claims and the ones granted by USPTO, so that applicants may make the appropriate corrections, if any.

As to the objection directed towards claim 26, the reply is "both". A pediatric dietary supplement is a dietary supplement intended for children. Therefore, it may contain nutritional elements/components particularly indicated for children. The invention is not limited to any particular form of administration, although the oral one is

preferred for children. Addressing the examiner's concerns, claim 36 is drafted to define the composition as in the form of a dietary supplement for children.

Humanized milk (correcting a typing mistake) is artificial milk for children which has been formulated with certain ingredients in order to make it as similar as possible to human milk (see for example US Patent 4,544,559 or 5,891,698).

Claim 38 specifies the bacteria are non pathogenic ones. This is consistent with the description found on page 4, lines 10-11 (*and their ingestion can be beneficial for the host*) or lines 20-21 (*to exert a dietetic, nutritional or therapeutic effect in an individual who needs it*). These definitions exclude pathogenic bacteria. In any event, a skilled reader will not put the invention into practice by using dangerous bacteria.

Applicant's description of the invention clearly states that one of the possible modes of carrying out the invention is by administering bacteria possessing high levels of alkaline sphingomyelinase (page 4, first full paragraph). On the other hand, the bacteria can be ingested either live or in the form of extracts (next paragraph). Therefore, the bacteria can be used both as delivery agents of alkaline sphingomyelinase (by ingesting them) and as source of the active ingredient (by extracting it from the bacteria). Climbing up the claim dependency, and not reading each claim as isolated, Claim 40 depends on Claim 39, which depends on Claim 35 (the main claim). The main claim provides the administration of alkaline sphingomyelinase, which can be of bacterial origin (Claim 38) and a list of possible bacteria is given in Claim 39, from which a preferred one is indicated (Claim 40). The rejection is believed to be in error. If the examiner's concerns are not already addressed in the above revised claims and/or this explanation and discussion, counsel is prepared to discuss different forms of expression if the examiner is not prepared to accept the current terminology.

Claim 31 - 35 U.S.C. § 112 - Deposit

Attached is a declaration of the undersigned permitting on grant access to deposit DSM 11988 made under the Budapest Treaty.

Having resolved the formalities issues attention is now directed to the prior-art based rejections stated on pages 8-15 of the Official Action. One rejection is based upon alleged anticipation and the other argues the previously considered claims lack patentability over the cited prior art. Both of these rejections are traversed having regard to the new and amended claims presented above as well as the following observations and comments taken together with information available to those of ordinary skill in the art as noted below.

Claims 25-30 and 32-34 - 35 U.S.C. § 102(b)

The reference US 5,716,615 will be addressed and compared with the presently claimed invention as far as it relates to the method of treatment, since such a method is claimed here, and not compositions. First, note that US '615 is directed to generic gastrointestinal disorders. Claim 35 discloses specific intestinal diseases, therefore a generic disclosure cannot anticipate a specific disclosure (see MPEP §2131.02).

US'615 specifically discloses diarrhoea, constipation, hypercholesteremia, endotoxin absorption or production of endogenous toxic substances (see the description) and chronic hepatitis (Example 1), and irritable bowel syndrome (Example 3). Disorders of the immune response and hypercholesterolemia have been deleted from Claim 35, thus rendering it novel over the cited US'615. This claim is of the *method-of-treatment* type, therefore, claiming a treatment of a disease A with a known composition, which was in the art used for treating disease B, is a novel treatment.

The disclosure of US 5,912,152 Hara et al is acknowledged. However, this reference relates to phospholipase C or sphingomyelinase from *Clostridium perfringens* and *Bacillus cereus*. This enzyme is different from alkaline sphingomyelinase (as demonstrated by the enclosed paper FEBS Letters by Goñi and Alonso, 2.1.5 and 2.1.6). The same argument applies to Sugimoto et al., wherein alkaline sphingomyelinase is not disclosed, it being appreciated that phospholipase is not alkaline sphingomyelinase.

As to the WO 98/22082 reference applied as an anticipation of previous claims 25, 29, 30 and 32-34 (but not claim 27), the first difference with the present invention is the

reference is limited to topical administration to skin and mucosae, whereas the present invention provides oral or parenteral administration. Claim 35 has been drafted by incorporating former Claim 27, which has consequently been deleted. This rejection is now moot.

Claims 25-34 - 35 U.S.C. § 103(a)

Claim 35 has been amended by changing the term inflammatory intestinal diseases to *acute* inflammatory intestinal diseases. This limitation teaches away from Sjokvist et al., who study *chronic* colitis with dysplasia. Dysplasia is associated with chronic colitis. Sjokvist et al. find that alkaline Smase activity was significantly reduced in patients with dysplasia compared to controls. No association was found between alkaline SMase activity and the degree of dysplasia. (See results). In the Table it will be observed that patients with no dysplasia, i.e. with acute colitis, have an alkaline Smase activity that the authors consider not dangerous to the patient. In fact, they conclude that low levels of alkaline Smase in chronic colitis with dysplasia "*may be a factor that impairs apoptosis in the mucosa and leads to uncontrolled cell proliferation*", namely to increased risk of colorectal cancer and dysplasia is a predictor, thus calling for a treatment.

There is no suggestion in Sjokvist, even when associated with the other cited references (discussed above), to administer alkaline Smase to subjects suffering from acute colitis, i.e. acute inflammatory intestinal diseases. Indeed, Sjokvist, et al., suggest no treatment.

In summary regarding the prior art references applied and the associated rejections based upon them, US'615, as discussed above, does not suggest to treat diseases based on low cellular content of alkaline Smase, but relates to generic gastrointestinal disorders, in particular disorders different from the ones treated in the present invention; WO'082 uses neutral Smase (see page 8, Results, Activity of Smase) which, as explained above is ineffective at intestinal alkaline pH; therefore the Examiner's assumption is not correct. Lastly, Sjokvist, et al., draw different conclusions with respect to the present claims and does not suggest administering alkaline Smase for acute inflammatory intestinal diseases.

For the above reasons it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and allowance are solicited.

Respectfully submitted,

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